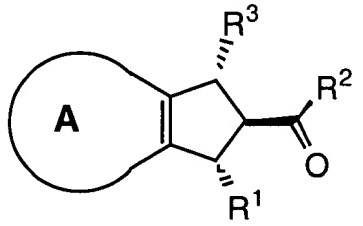
REMARKS

Claims 1 –30 are still pending. Applicants have amended Claim 1 to define cyclic "A" as 1) a 6-membered heterocyclyl containing one to three double bonds, but at least one double bond and optionally substituted with substituents as previously described or 2) an aryl as previously described in the specification on pages 8-11, 34-36 and 38. Thus, the changes are supported by the specification and are not new matter.

Novelty

The Examiner rejected Claims 1-30 under 35 U.S.C. 102(a) as allegedly anticipated by Tillyer et al U.S. 6,046,327 ('327) because the '327 reference allegedly teaches how to prepare cyclic compounds using a phosphate mediated cyclization process as in Applicants' Claims 1-30 (column 3, line 40 to column 4, line 76 and reaction schemes 1 and 4).

Applicants are claiming processes for preparing the compounds of formula I



I

and formula Ia using a *phosphoramide* reagent.

In contrast, the ' 327 reference restrictively discloses a process for preparing the compounds of formula I and Ia specifically using only a *chlorodi(C_1-C_4 alkyl)phosphate* reagent (claim 3 in Patent '327), not a *phosphoramide*. Consequently, the '327 reference cannot anticipate Claims 1-30 because the '327 reference does not disclose methods of preparing compounds of formula I using a *phosphoramide* reagent. Applicants respectfully request the rejection on this basis be withdrawn.

Enablement

The Examiner rejected Claims 1-30 under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains to make and use the invention.
To facilitate prosecution, Applicants have amended Claim 1 to define cyclic "A" as 1) a 6-membered heterocyclyl containing one to three double bonds, but at least one double bond and optionally substituted with substituents as previously described or 2) an aryl as previously described in the specification on pages 8-11, 34-36 and 38

Applicants respectfully traverse the rejection of Claims 1-30, specifically Claims 1-14 as amended and Claims 15-30 because, contrary to the Examiner's request for examples, the enablement requirement **does not require any examples**. Case law and the MPEP instead explicitly require an Examiner to justify why different compounds of a formula would require different techniques or process parameters. For example, in In re Strahilevi, the Examiner had alleged that because "of the breadth of the invention, a large number of examples would be required to enable one of ordinary skill in the art to make and use the invention." The Court of Customs and Patent Appeals expressly overruled the Examiner's unfounded and baseless demand for examples and held:

> "as acknowledged by the board, **examples are not required** to satisfy section 112, first paragraph. See, e.g., In re Stephens, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976); In re Borkowski, 57 CCPA 946, 422 F.2d 904, 164 USPQ 642 (1970); In re Gay, 50 CCPA 725, 309 F.2d 769, 135 USPQ 311 (1962). Therefore, the examiner's statement that the 'nearly universal applicability' alleged for the invention necessitated numerous examples was erroneous. Although the invention is applicable to a large variety of haptens and antigens, the **examiner offered no reason why these different compounds would require different techniques or process parameters**." In re Strahilevitz 668 F.2d 1229 (Cust. & Pat.App., 1982.)

Similar to the Examiner in In re Strahilevitz, the Examiner in Applicants' case did not justify why heterocyclic ring or rings as substituents or heterocyclic derivatives would require different process parameters. Consequently, by not justifying why heterocyclic ring or rings as substituents or heterocyclic derivatives would require different process parameters, the Examiner failed to demonstrate a lack of enablement.

Assuming arguendo that the Examiner had made a prima facie case of non enablement, the presumption is still rebutted, specifically regarding amended Claims 1-14 and Claims 15-30, because the specification does provide working examples of preparing compounds of formulas I and Ia.

Regarding Claims 1-14 which are drawn to the process for preparing the compound of formula I, the specification (on pages 34-36 and 38) provides a working example to enable one of ordinary skill in the art to prepare compounds of formula I when A is a heterocyclic that is optionally substituted. Regarding Claims 15-30 which are drawn to the process for preparing the compounds of formula Ia, the specification (on pages 25-26, and 29 (reaction schemes D-F) and pages 38-48) also provides a working example to enable one of ordinary skill in the art to prepare compounds of formula Ia.

Furthermore, the specification also provides working examples of a general methodology for generating the starting material for the claimed processes beginning from readily available

materials. For example, regarding Claims 1-14, the specification (on pages 34-36 and 38) provides a working example to enable one of ordinary skill in the art to generate the starting material Formula II (labeled as compound 9) beginning from readily available materials, such as compound 6. (Compound 6, on page 34 of the specification, is commercially available from Aldrich under order number D4,311-5.) Additionally, the specification, on pages 21-22, provides an alternative generic method for preparing precursors of starting material formula II by a coupling reaction at the position of ring A to give the starting material formula II.

Regarding Claims 15-30, the specification (on pages 25-26, and 29 (reaction schemes D-F) and pages 38-48) provides a working example to enable one of ordinary skill in the art to generate the starting material Formula IIa (labeled as compound 18, Example 10). Furthermore, Applicants respectfully contend that compounds of formula IIa (compound 18), where cyclic A is phenyl, pyrimidinyl or substituted versions of phenyl or pyrimdinyl, can be prepared from various analogs of compound 6 (Example 4), such as bromobenzene, 1,3-dibromobenzene, 4-bromopyrimidine, or 2,4-dibromopyrimidine. Applicants respectfully request the rejection on this basis be withdrawn.

Having addressed all the Examiner's rejections, Applicants respectfully request that the pending claims be allowed. If a telephone communication with the Applicants' representative will aid in prosecuting the instant application, please telephone the representative indicated below. Should any fees be due, the Commissioner is authorized to charge any fees required in connection with this amendment to Merck Deposit Account No. 13-2755.

Respectfully submitted,

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Date: November 18, 2002

CLEAN VERSION

IN THE CLAIMS

Please replace Claim 1 with the claim below:

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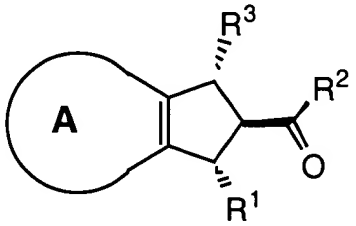
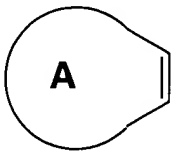
1. (Amended once) A process for preparing a compound of Formula I,



I

wherein:



represents:

(a) 6-membered heterocyclyl containing one to three double bonds, but at least one double bond and 1 to 3 heteroatoms selected from O, N and S, and the heterocyclyl is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, $(C_1\text{-}C_8)$-alkoxy, $(C_1\text{-}C_8)$-alkyl, $(C_2\text{-}C_8)$-alkenyl, $(C_2\text{-}C_8)$-alkynyl, $(C_3\text{-}C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$; or

(b) aryl, wherein aryl is defined as phenyl or naphthyl, which is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, $(C_1\text{-}C_8)$-alkoxy, $(C_1\text{-}C_8)$-alkyl, $(C_2\text{-}C_8)$-alkenyl, $(C_2\text{-}C_8)$-alkynyl, $(C_3\text{-}C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$, or when aryl is substituted on adjacent carbons they can form a 5- or 6-membered fused ring having one to three heteroatoms selected from O, N, and S, this ring being optionally substituted on carbon or

nitrogen with one to three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$, $(C_1$-$C_8)$-alkoxy, $(C_1$-$C_8)$-alkyl, $(C_2$-$C_8)$-alkenyl, $(C_2$-$C_8)$-alkynyl, $(C_3$-$C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

and wherein $(C_1$-$C_8)$-alkoxy, $(C_1$-$C_8)$-alkyl, $(C_2$-$C_8)$-alkenyl, $(C_2$-$C_8)$-alkynyl, or $(C_3$-$C_8)$-cycloalkyl substituent of aryl is further optionally substituted with one to three substituents
selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $OCPh_3$, $N(R^5)_2$, $(C_1$-$C_8)$-alkoxy, $(C_3$-$C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

A1 Cont.

R^1 is:

(a) $(C_1$-$C_8)$-alkyl, $(C_2$-$C_8)$-alkenyl, $(C_2$-$C_8)$-alkynyl, or $(C_3$-$C_8)$-cycloalkyl,

(b) aryl, wherein aryl as defined above, or

(c) heteroaryl, wherein heteroaryl is defined as a 5- or 6-membered aromatic ring containing one to three heteroatoms selected from O, N and S, and is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, $(C_1$-$C_8)$-alkoxy, $(C_1$-$C_8)$-alkyl, $(C_2$-$C_8)$-alkenyl, $(C_2$-$C_8)$-alkynyl, $(C_3$-$C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

R^2 is: OR^4 or $N(R^5)_2$;

R^3 is:

(a) $(C_1$-$C_8)$-alkyl,
(b) $(C_2$-$C_8)$-alkenyl,
(c) $(C_2$-$C_8)$-alkynyl,
(d) $(C_3$-$C_7)$-cycloalkyl,
(e) aryl, wherein aryl as defined above,
(f) heteroaryl, wherein heteroaryl as defined above,
(g) -CHO,
(h) -CO-$(C_1$-$C_8)$-alkyl,
(i) -CO-aryl,
(j) -CO-heteroaryl, or
(k) - CO_2R^4;

n is: 0 to 5;

R^4 is: H, or $(C_1\text{-}C_8)$-alkyl;

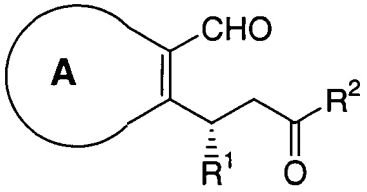
R^5 is: H, $(C_1\text{-}C_8)$-alkyl or aryl, wherein aryl as defined above;

R^6 is: H, $(C_1\text{-}C_8)$-alkyl or aryl, wherein aryl as defined above; and

R^7 is: H, $(C_1\text{-}C_8)$-alkyl, aryl or alkyl, wherein aryl is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, $(C_1\text{-}C_8)$-alkoxy, $(C_1\text{-}C_8)$-alkyl, $(C_2\text{-}C_8)$-alkenyl, $(C_2\text{-}C_8)$-alkynyl, $(C_3\text{-}C_8)$-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$, or when two R^7 substituents are on the same nitrogen they can join to form a ring of 3 to 6 atoms;

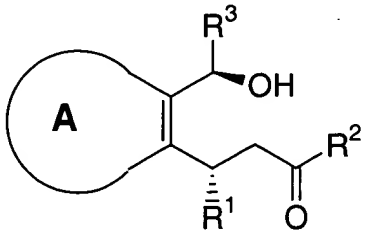
comprising the steps of:

(1) reacting a Grignard reagent with a conjugate adduct compound of Formula II,



II

in the presence of a first aprotic solvent and optionally an additive at a temperature range of about -80°C to about 30°C to give a Grignard addition product of Formula III; and



III

A1 cont.

(2) adding phosphoramide reagent to a mixture of the Grignard addition product of Formula III, a second aprotic solvent and a base at a temperature range of about -80°C to about 30°C to produce the desired compound of Formula I.